STUBBLEFIELD

Ethoxy-Valerianic Acid and some of its Derivatives

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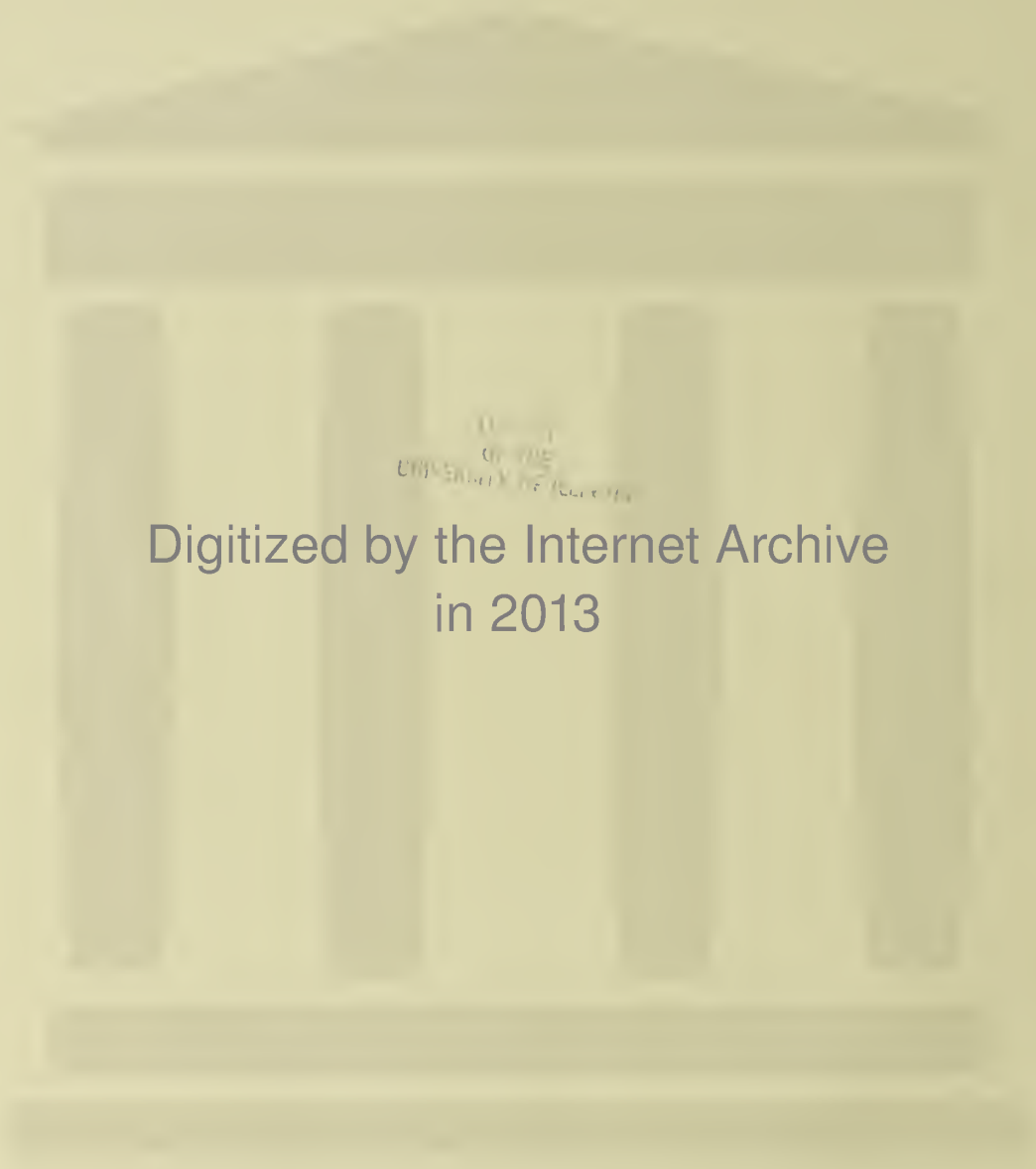

ETHOXY-VALERIANIC ACID

AND

SOME OF ITS DERIVATIVES

BY

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THESIS

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

BUFORD MATTHEWS STUBBLEFIELD

ENTITLED ETHOXY-VALERIANIC ACID AND SOME OF ITS DERIVATIVES

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry

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INTRODUCTION.

The distinction between pharmacological groups of anaesthetics and narcotics is important in practice, but does not depend upon a difference in the physiological action or chemical constitution. To produce general anaesthesia compounds which are volatile, and which are rapidly absorbed and excreted by the organism, are most suitable; on the other hand, less volatile liquid or solid substances, whose activity is slowly set free in the cells are more suitable for producing hypnosis. The latter condition can of course be produced by small doses of ether and chloroform, but the method of administration is objectional. On the other hand, narcotics like choral hydrate, if administered in large doses, may produce complete surgical anaesthesia. In fact, for a short while in the middle of the last century intravenous injections of choral hydrate were used in major operations. Its use was unsatisfactory because of the fact that the patient's safety was jeopardized by the large doses that had to be administered.

The aliphatic narcotics act first on the higher centers of the cerebrum; then on the lower centers of the medulla and cord, and finally on the reflexes. This behavior differentiates this group of narcotics from the alkaloidal narcotics of which morphine is a representative.

The aliphatic narcotics are divided chemically into several groups, chief of which are: the alcohols, aldehydes, ketones and their derivatives. Of the hydrocarbons it is

doubtful whether methane can be said to be a narcotic; however, ethane is a direct narcotic. The alcohols depend not upon the hydroxyl group but upon the hydrocarbon radicals for their narcotic action. An increase in the hydroxyl groups diminishes the narcotic activity.

The aldehydes depend upon the great chemical reactivity of the CHO group and the physiological properties of the alkyl groups for their physiological characteristics. Here again the hydroxyl group has a depressant action on the physiological activity of the compounds.

The ketones depend in the main on the presence of the alkyl radicals for their reactivity as narcotics and hypnotics.

The entrance of the carboxyl group into compounds of the aliphatic series reduces the toxicity and also reduces the narcotic action.

The aliphatic series is perhaps of more interest from a physiological standpoint on account of the alkyl radicals than it is for the individual compounds of the series. As has been stated before, the entrance of an aliphatic hydrocarbon radical has a pronounced effect upon the physiological reactivity of a compound. As has been shown by Fischer's work on the derivatives of barbituric acid the activity of these radicals increases as the molecular weight increases. With the propyl group the maximum physiological reactivity is attained, and from this point the activity begins to decrease. This is no doubt due in large part to the decrease in absorption by the animal organisms of bodies which have high

molecular weights.

While the propyl group is most active, the ethyl group seems to be best suited for use in compounds that are desired for their physiological reactivity because of the bad after effects that are prevalent after using a drug with the propyl group in it. The pronounced reactivity of the ethyl group is probably due to its affinity for the nervous system, as many substances containing this radical have pronounced hypnotic properties. The difference between the methyl and ethyl groups is shown in a group of sulphones whose hypnotic characteristics appear to depend entirely on the presence of the ethyl radical, since those containing the methyl group are quite inert. Amino phenol 1:2 has no hypnotic properties, but when the hydrogen of either the hydroxyl or the amino group is replaced by the methyl radical compounds with slight hypnotic effect result; thus:

C_6H_4 (O-CH_3, NH-CH_3) 1:2 and C_6H_4 (O-CH_3, $N(CH_3)_2$)

have slight narcotic properties, while the triethyl derivative has pronounced action C_6H_4 (O-C_2H_5, $N(C_2H_5)_2$).

The action of the ethyl group is increased when it is united to the parent substance thru oxygen. This linkage is not only advantageous because of the increased physiological reactivity but also because the solubility of the compound thus substituted is generally increased.

Another class of compounds that are of physiological interest is the substituted ammonias. Ammonia itself produces convulsions, but upon substitution this property is lost. However, formamide and acetamide are exceptions to this general behavior. These two compounds produce convulsions. With propionamide this action is less violent and with butyramide convulsions are rarely produced, and in these cases it is due to decomposition with the formation of ammonia. On the other hand butyramide has a pronounced narcotic action; this property decreases in the series until with formamide it disappears entirely.

In this work it was desired to produce an ammonium derivative containing both the propyl and the ethyoxy groups. Malonic ester was used as a foundation. The propyl group was first introduced by means of the malonic ester synthesis using propyl bromide. The ester thus obtained was saponified to the acid and one of the carboxyl groups removed by heating. The valerianic acid thus obtained was converted into the a-bromovalerianic acid by means of the Volhard-Zelinsky method. By treating with absolute alcohol the ester of a-bromovalerianic acid was obtained.

The ethyoxy group was next introduced by treating the bromoester with sodium ethylate. This reaction gives the ethyl ester of ethyoxyvalerianic acid. This ester was saponified and the free acid obtained.

The amide of the acid was produced by condensing the ester with ammonia. This gave the compound desired, the

physiological activity of which was studied by experiments on a dog. The amide proved to be a very good hypnotic and had no bad after effects.

PROPYL MALONIC ESTER.

To a solution of sodium ethylate, prepared by dissolving 28.1 g. of sodium (1 mol) in 350 cc. of absolute alcohol, 198 g. of malonic ester (1 mol) were added. After the reaction mixture had been cooled, 165 g. of propyl bromide (1 mol) were added. This addition was accomplished in six portions as considerable heat is evolved by the reaction. After all the bromide was added the mixture was heated until it reacted neutral to litmus. The alcohol was then distilled off on a brine bath and enough water added to dissolve the sodium bromide formed by the reaction. The ester, which separates as an oily layer, was extracted with ether. The ethereal solution was dried over calcium chloride, the ether removed and the ester fractionated. The fraction which boiled between 215°-225° was collected. The yield of ester amounted to 200 g., 80% of the theory.

SAPONIFICATION OF PROPYL MALONIC ESTER.

A concentrated solution of potassium hydroxide, 300 g. of alkali in 250 cc. of water, was used to saponify the ester. The alkali solution was placed in a flask provided with a reflux condenser and 255 g. of the ester were added in small portions through the condenser. It is necessary that the solution be kept hot and well agitated during the addition of the ester as the reaction becomes very violent if the ester is allowed to accumulate. After all the ester had been added the mixture was heated for an hour to insure complete saponification.

CALCIUM SALT OF PROPYL MALONIC ACID.

When the saponification was complete the solution was poured over 400 g. of crushed ice and made slightly acid by the addition of concentrated hydrochloric acid. Ammonium hydroxide was then added until the solution was faintly alkaline. Concentrated calcium chloride solution was then added in excess. Upon stirring the mixture the calcium salt separated out as a white voluminous mass. The salt was filtered off by the aid of suction and dried.

PROPYL MALONIC ACID.

The calcium salt obtained by the above procedure was placed in a beaker and a little water added. Concentrated hydrochloric acid was then added in about one third excess of the amount calculated as necessary to decompose the salt. The acid was extracted three times with ether, and the ethereal solution dried over anhydrous sodium sulphate. The ether was removed and the residue placed over sulfuric acid in vacuo. The yield of acid was about 75% or 120 g. The propyl malonic acid has a melting point of 96°.

VALERIANIC ACID.

The propyl malonic acid thus obtained was converted into valerianic acid by heating to 170° to remove the carbon dioxide. The valerianic acid obtained was fractionated and the portion boiling between 183°- 186° collected. The yield of valerianic from the propyl malonic acid was 95%, some of the acid being carried over by the escaping gas.

a-BROMOVALERIANIC ESTER.

Forty and eight tenths grams of valerianic acid (1 mol) together with 8.09 g. of red phosphorous ($\frac{1}{4}$ mol) were placed in a distilling bulb, the side arm of which had been bent up at an angle of about 30° and connected with a condenser, and 120 g. of bromine (11/6 mol) were slowly added from a dropping funnel, the stem of which had been drawn out to a capillary. To start the reaction the mixture was warmed on a water bath. After all the bromine had been added the mixture was heated on a water bath until the contents of the flask had become almost colorless. The bromacid after being cooled by holding the flask in running water, was slowly poured into 100 cc. of absolute alcohol. The flask containing the alcohol should be packed in ice as a great deal of heat is evolved during the reaction. The alcohol was used in a large excess, four times the amount required being used. The excess alcohol was evaporated off on the water bath and twice the volume of water added. Solid sodium carbonate was added until the mixture reacted alkaline to litmus. As soon as the mixture becomes alkaline the ester separates in an oily layer. The ester was separated and dried over calcium chloride. After filtration the ester was fractionated, the portion boiling between 185°- 190° was collected. A 60% yield amounting to 50 g. of the ester was obtained.

Later the procedure was changed somewhat. The amount of alcohol used was reduced by one half, thus

eliminating the necessity of evaporating off the alcohol. By this method considerable time was saved and the yield of ester was increased from 60 to 70%.

ETHYOXYVALERIANIC ESTER.

Fifty-two grams of bromovalerianic ester were added to a solution of sodium ethylate, prepared by dissolving 6.1 g. of sodium (1.05 moles) in 80 cc. of absolute alcohol. The ester must be added slowly as a good deal of heat is evolved. The reaction mixture was heated on the water bath for a while to insure complete reaction, the alcohol was then distilled off on a brine bath and enough water added to take up the sodium bromide formed. Upon adding the water the ester separated as an oily layer and was separated from the aqueous layer in a separatory funnel. One extraction with ether was made and the ester and ethereal solution dried over calcium chloride. The ether was removed and the ester fractionated, the portion boiling between 175° - 180° being collected. A yield of 85% or 37 g. of the ester was obtained.

When the ethyoxy ester was first prepared the bromo-ester was added to the sodium ethylate, but later, on account of mass action relationships, it was decided it would be best to add the sodium ethylate to the ester and thus prevent any possibility of saponifying the ester. By this method the yield was increased from 85% to 90%.

ETHYOXYVALERIANIC ACID.

To a solution of potassium hydroxide, prepared by dissolving 30 g. of potassium hydroxide in 150 cc. of water, 60 g. of ethyoxyvalerianic ester were added. When the saponification was complete 30 g. of ammonium chloride were added, the solution was then heated on the water bath until all the ammonia had been driven off. An excess of concentrated calcium chloride was then added, when the solution was stirred up the calcium salt settled out in a white flocculent mass. The salt was filtered off with the aid of suction and decomposed with concentrated hydrochloric acid. The acid was extracted with ether and the ethereal solution dried over sodium sulphate. The ether was removed and the acid fractionated. Collected from 220° - 225°. A yield of 70% or 35 g. of acid was obtained.

0.2850 g. subs. required 23.10 cc.,.085 N KOH.
Calc. for $C_7H_{14}O_3$ M.W. 146; found 145.1

AMIDE OF ETHYOXYVALERIANIC ACID.

Forty grams of the ethyoxy ester and 130 cc. of ammonia (Sp.G. 0.90) were sealed in a 250 cc. flask and placed on a shaker. At the end of two weeks of intermittent shaking the amide settled out in a white flocculent mass. The flask was opened and the amide filtered off and re-crystallized from water. A yield of 80% or 25 g. of the amide was obtained. The amide melted at 92.5°; is slightly soluble in cold and readily soluble in hot water, readily soluble in ether, alcohol or benzol.

0.3351 g. subs. gave 28.7 cc. N_2 (28°, 742.8 mm., over KOH). Calc. for $C_7H_{15}O_2N$:N, 9.65; found 9.72

PHYSIOLOGICAL ACTIVITY OF THE AMIDE.

The physiological properties of the amide with reference to its hypnotic properties were tried out. The tests were made on a dog weighing about thirty pounds.

In the first test, three grams of the amide were given to the dog. At the end of the first hour the animal showed signs of hypnosis and an hour and a half after the drug had been administered the animal passed into a light sleep which lasted for some time. At the end of three hours all apparent effect of the drug had passed off. At no time during the experiment did the dog show any signs of discomfort that could be attributed to the use of the amide.

On the following day a second trial was made. This time a dose of five grams was administered. At the end of the first hour signs of hypnosis were apparent. Two hours after the drug had been given the dog was in a sound sleep. The animal could not be roused from this without a great deal of effort. Even then the periods of stimulation were of short duration. At the end of the fourth hour the animal was apparently normal.